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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/270,910	03/16/1999	HANS HENRIK IPSEN	4305/1E144-U	3210

7590 05/20/2002

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	24

DATE MAILED: 05/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/270,910	Applicant(s) IPSEN ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

--The MAILING DATE of this communication appears on the cover she t with the correspondenc address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *Six* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *The amendment filed on 4/10/02 is a "draft"*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *2-14,16-28,32-34 and 47-50*.

   Claim(s) withdrawn from consideration: *29-31 and 40-46*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because:

The word "Draft" is on pages 2-12 of the amendement filed 4/10/02. The declaration by Piao King filed 4/10/2 is acknowledged.

Claims 48 and 50 stand objected to because of the following informalities: (1) the phrase "backbone tertiary of the naturally" as recited in claim 48 is missing the word "structure" and (2) The recitation of "(Asn for Thr at position 28, Lys for Gln at position 32, Glu to Ser at position 45, Asn for Ser at position 37, Glu for Ser at position 45, Pro for Gly at position 108 of SEQ ID NO: 37" are recited twice within the claim.

Claims 2-14, 32-34, and 47-50 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a recombinant birch pollen major allergen, Bet v I from the taxonomic order of Fagales wherein said recombinant allergen has an amino acid substitution from glutamine to serine at position 45 of the natural Bet v I, and vaspid venom Ves v5, does not reasonably provide enablement for any recombinant allergen such as inhalation allergen from the taxonomic order of Oleales, Pinales, Asterales, Urticales, allergen from a house dust mite originating from Dermatophagoides, cockroach allergen, or animal allergen originating from a cat, dog or horse for a pharmaceutical composition or a vaccine comprising said recombinant allergen against allergic reaction elicited by a naturally occurring allergen in patients suffering from allergy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant's arguments filed 7/13/01 have been fully considered but they are not persuasive.

Applicants' position is that the specification provides detailed examples of how to make and use two very different source of allergen, i.e., inhalation allergen from birch pollen antigen Bet v1 and vaspid venom Ves v5 and the method of obtaining the mutant allergens as taught in the specification may be applied to a wide range of allergen from various source. Applicants further state that it is not necessary to provide in vivo data for pharmaceutical compositions and vaccine.

However, the amendment does not overcome the rejection for the reasons stated below.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses only recombinant birch pollen major allergen, Bet v I (SEQ ID NO: 37) from the taxonomic order of Fagales wherein said recombinant allergen has an amino acid substitution from Thr to Pro at position 10, from Asp to Gly at position 25, Asn for Thr at position 28, Lys for Gln at position 32, Glu to Ser at position 45, Asn for Ser at position 37, Lys for Asn at position 55, Thr for Ala at position 77, Pro for Gly at position 108 (page 27 of specification) and vaspid venom Ves v5 having amino acid substitution from Lys to Ala at position 72 and from Tyr to Ala at position 96 of SEQ ID NO: 39 (See pages 44-45).

Besides the specific recombinant birch pollen major allergen Bet v I and vaspid venom Ves v5 mentioned above, the specification fails to provide any guidance as how to make and use recombinant mutant allergen such as inhalation allergen from the taxonomic order of Oleales, Pinales, Asterales, Urticales, allergen from a house dust mite originating from Dermatophagoides, cockroach allergen, or animal allergen originating from a cat, dog or horse in which at least one surface-exposed amino acid residues of a B cell epitope at a position which is conserved in the amino acid sequences of homologous proteins within the taxonomic order from which the naturally occurring allergen originates is substituted with an amino acid residue which is not conserved in the same position wherein the recombinant mutant allergen has an a-carbon backbone tertiary structure essentially the same as the a-carbon backbone tertiary structure of the naturally occurring allergen and specific IgE binding to the mutant allergen is reduced compared to the IgE binding to the naturally occurring allergen wherein the specific IgE binding to the mutant is reduced by at least 5%, preferably at least 10% wherein at least one patch of conserved amino acid residues comprises atoms of 15-25 amino acid residues ranked with respect to solvent accessibility and one ore more amino acids among the more solvent accessible ones are substituted for a pharmaceutical composition or a vaccine.

There is insufficient guidance as to determine which amino acid residues and the specific type of amino acid within the full-length amino acid sequence of any recombinant allergen mentioned above which can be substitute and whether after amino acid substitutions would maintain the a-carbon backbone tertiary structure and reduced IgE binding at least 5%, or at least 10% as compared to the naturally occurring allergen for a pharmaceutical composition or a vaccine against said allergen. The term "comprises" is open-ended. By reciting the term "comprises" atoms of 15-25 amino acid residues in the claim, the amino acid sequence encompasses indefinite number and type of additional amino acids, in addition to the 15-25 amino acid residues as recited in the claim. It is well known in the art that the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495).

The state of the prior art as exemplified by Lebecque et al, Gajhede et al and Elsayed et al (all of record) is such that determining the IgE binding of Bet v 1 (B cell epitope) is conformational dependent by nature, including applicants' disclosure on page 36 bridging to page 37. Given the diversity of B cell epitope ranging from conformational to linear epitope structures, there is no predictability regarding what effect amino acid substitutions will have on the structure and function of all allergen mentioned above because it is difficult to predict the 3-D structure of modified allergens and the resulting binding of IgE in vivo. The predictability of making modified allergens mentioned above is limited to factors such as the mutagenesis method. Given the insufficient guidance and working examples, predicting what changes can be made to the amino acid sequence of any allergen mentioned above that after substitution, will retain both structure and reduce IgE function in vivo is unpredictable. Since the specification fails to provide guidance regarding which amino acid can tolerate change, it follows that any allergen mentioned above other than Bet v I from the taxonomic order of Fagales is not enable. With regard to a pharmaceutical composition and vaccine comprising said allergen for treating allergy, since IgE-binding properties of any of the recombinant mutant allergen mentioned above have not been demonstrated, it is inconceivable any of the recombinant allergen mentioned above would be useful as a pharmaceutical composition or a vaccine. Even if IgE binding is reduced by 5% or

by 10%, there is still a 95% or 90% chance that the mutant allergen will bind IgE. Further, in the absence of in vivo data, is unpredictable for the following reasons: 1) the protein may be inactivated before producing an effect, for instant, due to proteolytic degradation or immunological inactivation as a consequence of the inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment and (4) the route of administration and effective doses have not been demonstrated. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).
Furthermore, the specification fails to provide guidance as to which part of the a-carbon backbone tertiary structure of the allergen molecule is essentially preserved since the phrase "overall" as recited in claim 2 has been deleted.
For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Claims 2-14, 16-28, 32-34, and 47-50 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
The recitation of "essentially" in Claims 2 (C) and 48 is indefinite and ambiguous. It is unclear what are the metes and bounds of the term "essentially". It is suggested that the term "essentially" be deleted in the claims.
The recitation of "Lys72A or Tyr96A1a" in claim 28 is ambiguous. It is suggested that Applicants amend the claim to recite "from Lys to Ala at position 72 or Tyr to Ala at position 96", for example.

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